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Malformations of cortical development (MCDs) and epilepsy: Experience from a tertiary care center in south India

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ABSTRACT

Introduction: Malformations of cortical development (MCDs) are increasingly recognized as important cause of epilepsy, especially refractory epilepsy. In developing countries like India, where the facilities for sophisticated imaging are not easily accessible to all, the prevalence and the types of cortical malformations are largely unknown. Hence this preliminary study has been undertaken to examine the relation between epilepsy and malformations of cortical development in a resource-limited setting.
Aims: To study various types of malformations of cortical development (MCDs) associated with epilepsy and to correlate with their clinical semiology.
Settings and design: The study was conducted in a tertiary care neurological center in south India. Cohort included all patients with epilepsy associated with cortical malformation on neuroimaging.
Methods and materials: Neuroimaging data of all patients with epilepsy were evaluated for a 5-year period from 1998 to 2003, for the presence of cortical malformations. The case records of those patients with cortical malformations were taken from the medical records department and the clinical and electrophysiological data were analyzed.
Results: We are reporting 34 cases of MCDs evaluated during the 5-year period. The mean age of the cohort was 15.1 (±12.2) years, with a range from 3 months to 45 years and 52.9% were males. Mean age at seizure onset was 7.2 years (±7.8), with a mean duration of seizure of 8.1 years (±7.7). Delayed motor and mental milestones were present in 15 patients (44.1%) and positive family history of seizure/epilepsy was seen in 9 patients (26.5%). Cortical malformations were most often associated with partial seizures (19/34, 55.9%). The most common type of seizure was complex partial seizure, seen in 12 patients (35.3%). Majority had very frequent, uncontrolled seizures with 16 (47.1%) patients having a seizure frequency of more than one per day. Heterotopias were seen in 14 patients (41.2%), in isolation in 5 (14.7%) patients and in combination with other malformations in 9 (26.5%) patients. Pachygyria was present as an isolated anomaly in five (14.7%) patients and combined with other abnormalities in eight (23.5%) patients. Cortical dysplasia was seen in 5 (14.7%) patients, hemimegalencephaly in two patients, polymicrogyria in two patients, lissencephaly and schizencephaly were seen in one patient each. EEG demonstrated focal epileptiform discharges in 59.1%, while generalized epileptiform discharges were seen in 22.7% of patients. Twenty-seven out of 34 (79.4%) patients had refractory/difficult to treat epilepsy.
Conclusions: Malformations of cortical development are a heterogenous group of disorders, associated with developmental delay and refractory seizures but seizures usually do not have pathognomonic semiologic features. Possibility of MCDs should be considered during the evaluation of refractory epilepsy cases.

1. Introduction

Malformations of cortical development (MCDs) are increasingly recognized as important cause of epilepsy, especially refractory epilepsy.[1] They were earlier identified only at postmortem examination of subjects with gross developmental disorders or with severe childhood epilepsy.[2] Now the scenario has changed due to the availability of newer and sophisticated imaging techniques such as computed tomography (CT) and high-resolution magnetic resonance imaging (MRI). Many of the cases initially considered as idiopathic or cryptogenic epilepsy are now found to be secondary to developmental malformations of the cortex.[3]

The true prevalence and incidence of cortical malformations associated with epilepsy is unknown, since MCDs causing easily treatable epilepsy may remain undiscovered unless all patients

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with epilepsy are subjected to neuroimaging (MRI) using appropriate techniques. In countries with limited resource settings like India, where the facilities for sophisticated imaging are not easily accessible to all, the prevalence and the types of cortical malformations are largely unknown. Hence this preliminary study has been undertaken to examine the relation between epilepsy and malformations of cortical development.

2. Subjects and methods

This study was conducted in a tertiary care neurological center (National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore), which caters to epilepsy patients, especially those from southern parts of India. Neuroimaging data of all epilepsy cases were analyzed over a 5-year period for the presence of MCDs. The case records of patients found to have cortical malformations on neuroimaging were taken for further analysis. Those with cortical malformations on imaging without any seizures, dysembryoplastic neuroectodermal tumors and patients with tuberous sclerosis were excluded from the study. Detailed clinical and electrophysiological data were prospectively collected from the patient/care giver with special reference to

1. The antenatal, perinatal and postnatal events.
2. Developmental milestones.
3. Family history of seizures.
4. Type and frequency of seizures.
5. The number of medications used (as a measure of refractoriness).

These data were entered on to a pre-designed clinical proforma.

2.1. MRI protocol

MR imaging was done using a 1.5 T, GE scanner. Protocol included SE (Spin Echo) T1W image, TSE (Turbo Spin Echo) T2W image and SPGR (Spoiled Gradient Recalled) sequence of brain in orthogonal planes. All scans were evaluated by an experienced neuroradiologist (SSG). Patient's clinical characteristics were correlated with neuroimaging findings.

2.2. Statistical analysis

Both clinical and neuroradiological data were entered into the SPSS 10, software package for descriptive statistics. Results of the study are expressed as mean with standard deviation and range, for continuous variables and as percentages for discrete variables.

3. Results

During the study period from 1998 to 2003, we encountered 34 cases of cortical malformations with epilepsy. In the year 2003, 220 MRI scans were done for patients with diagnosis of epilepsy/seizures, at NIMHANS and of this, 10 cases (4.5%) of cortical malformation and epilepsy were identified. Diagnosis of cortical malformation was made by either CT or MR imaging, in 30 out of 34 patients. Majority of the patients were diagnosed on the basis of MR imaging (79.4%). In two patients diagnosis was established postoperatively and in the other two at postmortem, by pathological examination.

3.1. Age and sex distribution

The mean age of the study group was 15.1 ± 12.2 years. The youngest of the cohort aged 3 months while the oldest was 45 years. Majority of the patients belonged to the second or third decade. Of the cohort, 18 (52.9%) were males and 16 (47.1%) were females.

3.2. Antenetal, perinatal events and milestones

There was no history of any antenatal maternal infection or drug exposure. Twenty-seven (79.4%) patients had normal vaginal delivery while remaining seven had lower segment caesarean section. Only three patients had history of delayed first cry. Delayed motor and mental milestones were noted in 15 patients (44.1%).

3.3. Family history

Family history of consanguinity was present in four patients and history of seizure/epilepsy was present in nine patients (26.5%). Among this cohort there was one pair of heterozygous twins with cortical malformation affecting both the twins.

3.4. Examination

General physical examination and neurological examination were normal in 22 out of 34 (64.7%) patients. Concomitant squint was noted in three patients, right hemiparesis in 2, microcephaly in 2, generalized hypertonia in 2, dysmorphic facies in 2 and paraparesis in 1.

3.5. Seizure type

Cortical malformations were most often associated with partial seizures (19/34, 55.9%). The most common type of seizure was complex partial seizure, which was seen in 12 patients (35.3%). In 10 patients with complex partial seizures there was history of secondary generalization. Seven (20.6%) patients had simple partial seizures. Of the seven patients who had generalized seizures, four were generalized tonic–clonic seizures, two were generalized tonic seizures and one had myoclonic seizure. Eight (23.5%) patients had multiple types of seizures. Median age of seizure onset was 5 years, with a range from 1 month to 27 years. Duration of seizures ranged from a minimum of 1 month to a maximum of 38 years. The mean duration of seizure was 8.1 years ($\pm$7.7 years).

3.6. Seizure frequency

Majority had very frequent, uncontrolled seizures with 16 (47.1%) patients having a seizure frequency of more than one per day. Two patients had seizure frequency of more than one per week, while eight patients had seizure frequency of one or more per month. Of the remaining eight patients, five had occasional seizures and data regarding seizure frequency were unavailable in three patients. Majority of them had refractory complex partial seizures.

3.7. Status epilepticus

Three (8.8%) patients had status epilepticus and all three expired. Partial autopsy was done in two patients. One patient had polymicrogyria in the occipital region and another one had heterotopia in the left parietooccipital region. Third patient had left frontal cortical dysplasia on neuroimaging.

4. Neuroimaging

4.1. Magnetic resonance imaging

MR imaging was available in 29 (85.3%) patients. Diagnosis of cortical malformation was established by brain MRI in 27 out of 29 subjects in whom it was done (93.1%). In other two patients though

Table 1
MRI Findings in patients with MCDs.

MRI brain ($n=29$) (malformations)	Number (%)
Heterotopias	4 (13.8)
Pachygyria	5 (17.2)
Cortical dysplasia	4 (13.8)
Hemimegalencephaly	2 (6.9)
Polymicrogyria	1 (3.4)
Lissencephaly	1 (3.4)
Schizencephaly	1 (3.4)
Multiple abnormalities	9 (31.0)
Cystic lesion[a]	2 (6.9)

[a] One patient had cortical dysplasia and other had heterotopia on postoperative histopathological examination.

Table 2
Multiple anomalies on MRI.

Multiple anomalies ($n=9$)	Number
Pachygyria with band heterotopia	3
Pachygyria with nodular heterotopia	2
Pachygyria, polymicrogyria, nodular heterotopia	2
Pachygyria with corpus callosal agenesis	1
Nodular heterotopia with corpus callosal agenesis	1

MRI was abnormal, diagnosis of malformations of cortical development was made only postoperatively, after histopathological examination. MRI findings in this cohort are shown in Table 1. In patients with multiple abnormalities (31%) commonest finding was a combination of band heterotopia and pachygyria (Table 2). Heterotopias were seen in isolation in four patients (13.8%) and in combination with other malformations in eight patients (27.6%). Out of these 12 patients with heterotopias, band heterotopia ('double cortex') was seen in 3 patients. Pachygyria was present as an isolated anomaly in five (17.2%) patients and combined with other abnormalities in eight (27.6%) patients. Commonest associated abnormality with pachygyria was band heterotopia.

4.2. Computed tomography

CT scan was done in 25 (73.5%), of which 21 (84%) were abnormal and 4 (16%) were normal. Out of the 21 abnormal scans, 12 (57.1%) had non-specific CT findings, 6 had pachygyria, 1 had schizencephaly, 1 had hemimegalencephaly and lissencephaly was seen in 1. In two patients diagnosis of cortical malformations was based only on CT findings, as MRI was not available. Of these two patients one had schizencephaly and another lissencephaly. Commonest abnormality that was found on CT scan was pachygyria (six patients). MRI of these six patients, confirmed the presence of pachygyria, but in three of them, additional abnormalities like heterotopias (2) and hemimegalencephaly (1) were detected on MR imaging.

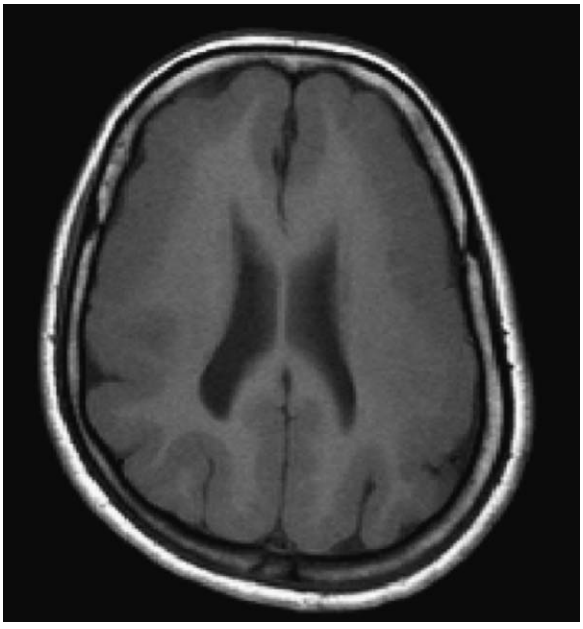

Fig. 1. MRI brain (Flair) showing agyria–pachygyria complex in a 8-year-old female and generalized tonic seizure.

4.3. Cortical localization of MCDs

Ten out of 34 patients (29.4%) had bilateral or diffuse abnormality of the cortex. MCDs were located in the frontal lobe in five patients. It was temporal in five patients, parietal in three patients and occipital in three patients. In the remaining, multiple lobes were involved, frontoparietal area being the commonest (23.5%).

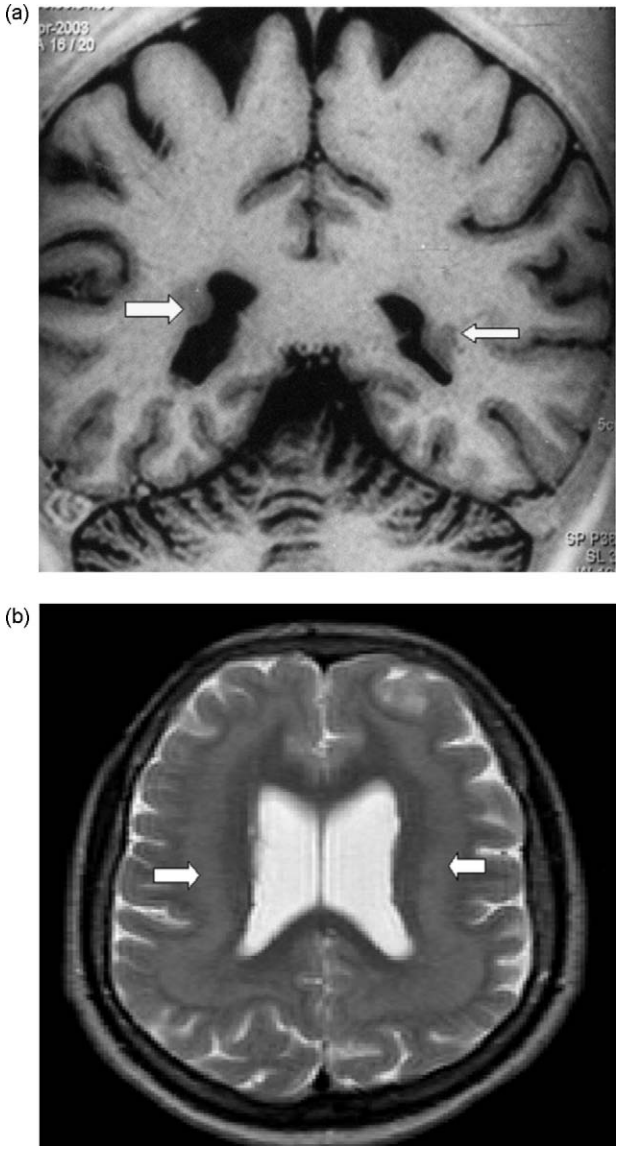

Fig. 2. (a) MRI brain (Flair) showing periventricular nodular heterotoia (white arrow) in a 20-year-old female with complex partial seizure. (b) MRI brain T2W image showing band heterotoia (white arrow) in a 7-year-old female with generalized seizure.

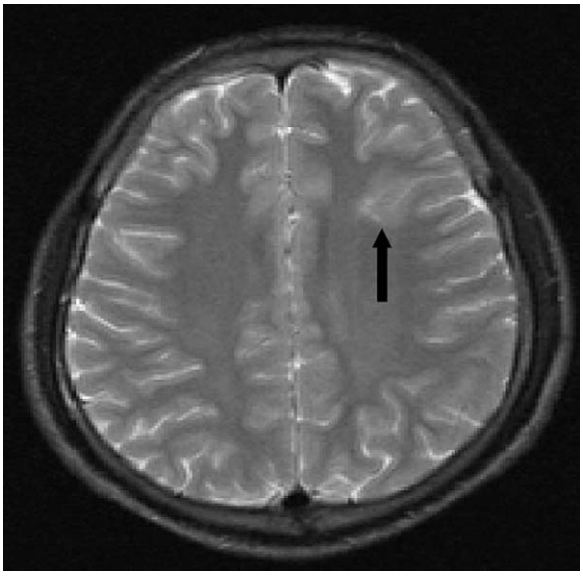

Fig. 3. MRI brain showing focal cortical dysplasia (black arrow) in a 16-year-old male with complex partial seizure.

4.4. Distribution of malformations of cortical development

4.4.1. Pachygyria

Of the five patients with isolated pachygyria, parietal lobe was involved in two patients, frontotemporal region in one patient and diffuse involvement in two patients (Fig. 1).

4.4.2. Heterotopias

Heterotopias were diffuse in three patients, temporal in one patient and parietooccipital in one patient (Fig. 2a and b).

4.4.3. Cortical dysplasia

Of the four patients with cortical dysplasia on MRI, three were in the frontal lobe and one in the frontoparietal region (Fig. 3). In one patient in whom cortical dysplasia was diagnosed postoperatively, the dysplasia was located in the right temporal region along with medial temporal sclerosis ('dual pathology').

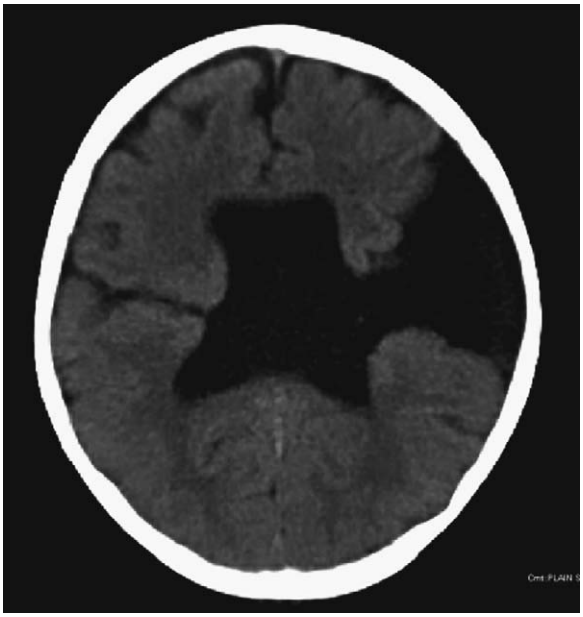

Fig. 4. CT brain showing bilateral open lip schizencephaly in a 4-year-old male with audiogenic myocloic jerks.

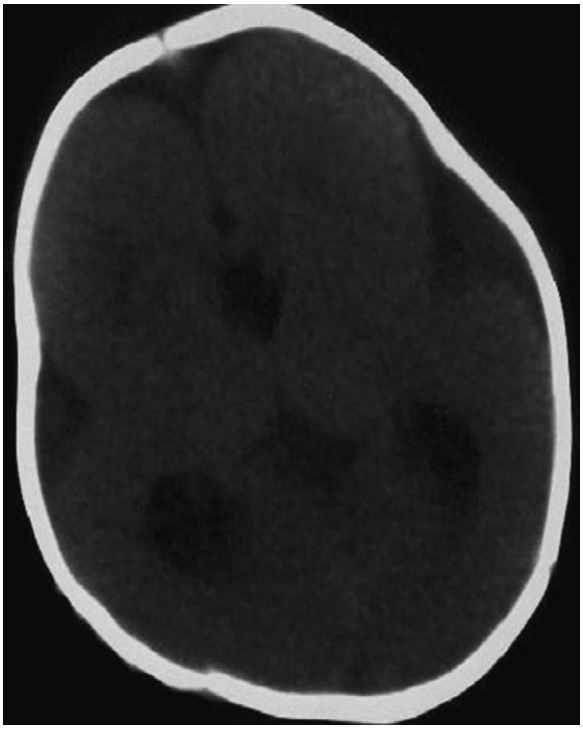

Fig. 5. CT brain showing lissencephaly ("smooth brain") in a 3-month-old infant with generalized tonic seizures.

4.4.4. Schizencephaly

In the patient with schizencephaly the cleft was located in the frontoparietal region (Fig. 4).

4.4.5. Lissencephaly

In the single patient with lissencephaly cortical involvement was diffuse (Fig. 5).

4.4.6. Hemimegalencephaly

Two patients with hemimegalencephaly had involvement of the left cerebral hemisphere (Fig. 6).

4.5. EEG

Scalp EEG was available in 22 (64.7%) patients. Among this, five patients had generalized epileptiform discharges. Four out of five patients with generalized epileptiform discharges had either diffuse or multiple malformations of cortical development. One patient with left frontoparietal cortical dysplasia had generalized seizure discharges. Of the 13 patients who had focal epileptiform discharges, 5 patients had bilateral/diffuse abnormality. In one patient there was discordance between the site of focal epileptiform discharges and the anatomical area of abnormality as evidenced by the MRI scan. EEG was normal in four patients, two with focal pachygyria and two with nodular heterotopia (one focal and one multiple subependymal nodular heterotopia). Correlation between focal EEG abnormalities and MRI findings are poor and given in Table 3.

4.6. Treatment

Twenty-seven out of 34 patients had refractory/difficult to treat epilepsy. Seizures were apparently controlled with one AED in

Table 3
Correlation of focal EEG abnormalities and MRI findings.

EEG—focal discharges	MRI brain	Anatomical site of radiological MCDs
Right hemispheric discharges	Nodular heterotopia	Diffuse
Left hemispheric discharges	Schizencephaly	Bilateral left > right
Right anterior temporal focus	Nodular heterotopia + pachygyria	Diffuse
Left frontotemporal focus	Cortical dysplasia	Left frontal
Left centrotemporal focus	Nodular heterotopia + pachygyria	Right frontal
	Hemimegalencephaly	Left hemisphere
Bilateral frontal foci	Pachygyria	Diffuse
Right temporal focus	Cortical dysplasia	Right temporal
Left hemispheric discharges	Pachygyria	Diffuse
Multifocal	Pachygyria	Right parietal
Left temporal focus	Cortical dysplasia	Left frontal
Left temporal focus	Pachygyria	Left frontotemporal
Right temporal focus	Cortical dysplasia	Right temporal

seven patients. Twenty-seven (79.4%) patients were on two or more antiepileptic drugs, of which 74.1% received three AEDs.

4.7. Autopsy

Postmortem examination of the brain was available in two cases, who had succumbed to status epilepticus. CT scan in both of them had shown diffuse cerebral odema, probably secondary to acute status epilepticus. One patient had polymicrogyria in the left occipital region and another had heterotopia in the left parietooccipital region. In two patients who had a cystic lesion in the right temporal region on MRI, underwent surgery. Postoperative specimen was available in these two. Histopathological examination revealed the presence of cortical dysplasia in one and nodular heterotopia in another. These were not evident on MR imaging.

5. Discussion

In this cohort, we had 34 cases of cortical malformation and epilepsy. We had excluded cases with cortical malformations on imaging without any seizures, those with dysembryoplastic neuroectodermal tumors (DNET) and patients with tuberous sclerosis (TS). In the year 2003, of the 220 MRI scans done for patients with diagnosis of epilepsy/seizures, at NIMHANS, 10 cases of cortical malformations (4.5%) were identified. Brodtkorb et al.[4] did a retrospective study among 303 patients with epileptic seizures referred for magnetic resonance imaging. During a 3-year period they found 13 patients with neuromigrational disorders (4.3%). Li et al.[1] reported the MRI findings in 341 patients referred with chronic refractory epilepsy, from 1991 to 1994 and they reported cortical dysgenesis in 12% of their cases.

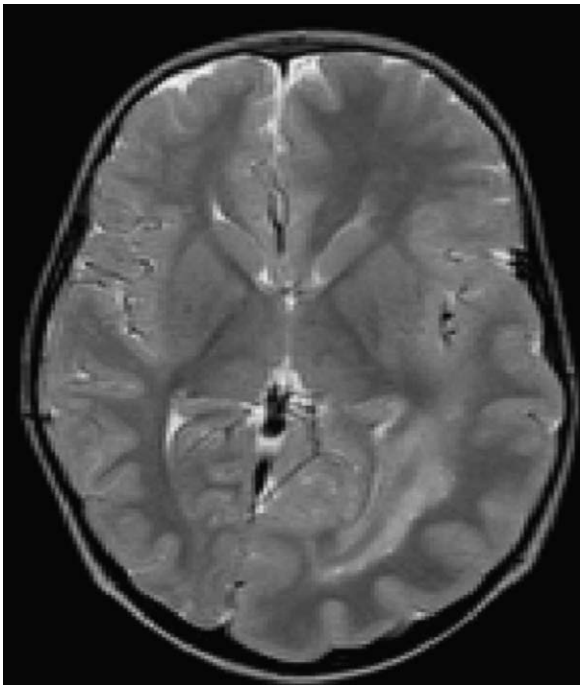

Fig. 6. MRI brain showing left hemimegalencephaly in a 6-year-old female with right focal seizure.

None of the patients had history of any antenatal maternal infection or drug exposure in our cohort similar to the observations of Brodtkorb et al.[4] Delayed motor and mental milestones were present in 15 patients (42.9%). In the series of Raymond et al.[5] delayed milestones were present in only 10% of the individuals. Family history of seizure/epilepsy was present in nine patients (26.5%) in the current study. Raymond et al.[5] found family history of epilepsy in 20% of their cases.

The most common type of seizure in the current study was partial seizures, especially complex partial seizure. In the study by Raymond et al.,[5] 84% had partial seizures and 16% had generalized seizures. Among 13 patients in the series of Brodtkorb et al.,[4] 3 had complex partial seizures, 1 had generalized tonic–clonic seizure and 9 had multiple types of seizure. Most common was a combination of simple partial seizure and generalized tonic–clonic seizure, which was seen in five patients.[4]

Neuroimaging, especially high-resolution MR imaging, is of paramount importance in detecting malformations of cortical development (MCDs). Gross abnormalities such as lissencephaly or schizencephaly may be identified on CT scan. CT scan though not considered as an ideal investigational method for MCDs was abnormal in about 84% of patients in whom it was done. This is probably because of newer generation spiral CT machines and increased awareness among neurologists and neuroradiologists. But out of the 21 abnormal scans, 12 (57.1%) had non-specific CT findings, indicating the poor yield of CT in patients with cortical malformations. Diagnosis of cortical malformation was established by brain MRI in 27 out of 29 subjects in whom it was done (93.1%). Majority of the patients (31%) had multiple abnormalities on MR imaging, the commonest being a combination of pachygyria and heterotopia. In the study of MCDs, among intractable focal epilepsy, by Janszky et al.,[6] nine patients had focal cortical dysplasia, followed by heterotopia in six patients and pachygyria in six patients. Heterotopias were the commonest abnormality in the series of Raymond et al.,[5] while schizencephaly being the commonest finding in the series of Brodtkorb et al.[4] Differences between different case series probably reflect selection bias rather than true frequencies.

Focal epileptiform discharges were the commonest EEG abnormality but there was no specific pattern consistent with the findings of other studies.[2,5] EEG should be seen as an investigational tool, but not one that defines the condition.[2] But this along with video EEG could be used while planning for surgical mode of treatment of MCDs. We do not have video EEG data in this cohort as this facility was not available then. Twenty-seven out of 34 (79.4%) patients had refractory/difficult to treat epilepsy and were on two or more antiepileptic drugs. Nearly three-fourth of them received three or more medications, indicating the refractoriness of seizures in this class of patients. Malformations of corical development are known for their intrinsic epileptogenicity and refractoriness. Aronica et al.[7] and Spalice et al.[8] reported that there is high expression of metabotropic glutamate receptors (mGluRs) especially mGluR1α and mGluR5 in the dysplastic neurons, suggesting a possible contribution of glutamate receptors in the intrinsic and high epileptogenecity of dysplastic cortical regions.

6. Conclusion

Malformations of cortical development are a heterogeneous group of disorders. They may be associated with developmental delay, seizures with or without family history, but do not usually have pathognomonic semiologic features. MCDs are usually well demonstrated by high-resolution MR imaging, but may require sophisticated imaging techniques to reveal their complete extent. Epilepsy caused by MCDs usually responds poorly to medical management. Surgery may be a better option for the carefully selected patients but this requires extensive pre-surgical evaluation and good surgical skill. Malformations of cortical development are an area of active research especially in the field of imaging and genetics and there are rapid developments. In future we may have better diagnostic and therapeutic options for this group of patients with MCDs.

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